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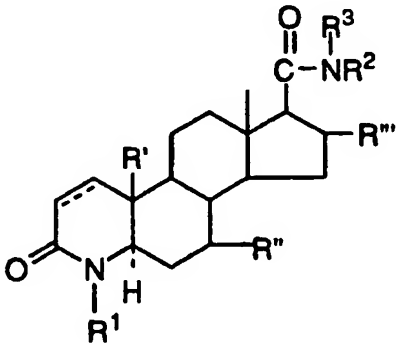

(I)

(57) Abstract

17β-N-substituted-carbamoyl-4-aza-5-α-androst-1-en-3-ones of formula (I), wherein the dotted line represents a double bond when present and R^1 and R^3 are independently selected from hydrogen, methyl and ethyl and R^2 is a straight or branched chain substituted or unsubstituted alkyl, cycloalkyl, aralkyl of from 1-12 carbons, or monocyclic aryl optionally containing 1 or more lower alkyl substituents of 1-2 carbon atoms and/or 1 or more halogens, and R', R'', R''' are hydrogen or methyl, with the proviso that R^2 is not t-butyl where R^1 and R^3 are H, are useful in combination therapy with minoxidil for treating patterned alopecia, male pattern baldness, female pattern alopecia, alopecia senilis or alopecia areata.

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TITLE OF THE INVENTION

COMBINATION METHOD FOR TREATING PATTERNED ALOPECIA WITH 17β-N-SUBSTITUTED-CARBAMOYL-4-AZA-5α-ANDROST-1-EN-3-ONES AND MINOXIDIL

BACKGROUND OF THE INVENTION

The present invention is concerned with the use of 17β-N-substituted-carbamoyl-4-aza-5α-androst-1-en-3-one compounds as testosterone-5α-reductase inhibitors in combination with minoxidil for the treatment of patterned alopecia, i.e., male pattern baldness.

Baldness or alopecia, in addition to male pattern alopecia, female pattern alopecia, and alopecia senilis, includes alopecia areata, and further, diseases accompanied by basic skin lesions such as cicatrix or infectious tumors, or accompanied by systemic disorders, for example, an internal secretion abnormality or nutritional disorder.

Also, concerning alopecia areata, it is considered that an autoimmune phenomenon participates therein, and therefore, the administration of a substance having an immunosuppressive action can have therapeutical effect on alopecia areata.

The causes of human pattern alopecia (also called "androgenic alopecia") and alopecia senilis are considered to be: an activation of male hormones at organs such as hair roots and the sebum gland; a lowering in the amount of blood reaching the hair follicles; a scalp abnormality caused by an excessive secretion of sebum, a formation of peroxides, or a propagation of bacteria; genetic causes; and aging.

Hair revitalizing materials of the prior art generally comprise compounds having the actions of removing or alleviating the causes mentioned above formulated therein. For example, a compound having the action of inhibiting the activation of male hormones, or a compound having the action of increasing the amount of blood reaching the hair follicles, is formulated.

Nevertheless, in human pattern alopecia and alopecia senilis, the epilation mechanism and the hair generation mechanism are very complicated, and by merely inhibiting an activation of male hormones or increasing the amount of blood reaching the hair follicles, as practiced in the prior art, does not sufficiently treat or prevent baldness or alopecia. Accordingly, there is a long-felt need for a hair revitalizing agent for male pattern alopecia and alopecia senilis, which provides satisfactory results.

Patterned baldness is sometimes called androgenic alopecia because male hormones are necessary for its development. It does not occur before adolescence, nor in castrates. Attempts to prevent alopecia by hormonal treatments by using anti-androgens or female hormones have failed. A hereditary component is also recognized since patterned alopecia runs in families. Despite intensive investigation, the mechanism whereby terminal follicles convert to vellus ones is unknown.

The topical application of minoxidil is currently the most effective therapy for patterned alopecia. Minoxidil is a well-known pharmaceutical agent marketed by The Upjohn Company in the form of LONITEN® Tablets for the treatment of hypertension. Numerous investigators have demonstrated that it can stimulate visible hair growth in a majority of balding subjects. The structure and use of this compound is described in U.S. Pat. Nos. 4,139,619 and 4,596,812. This compound has varying degrees of efficacy for moderating androgenic alopecia, depending on the degree of baldness, its duration, the age of the patient and, of course, on the concentration of the drug in an appropriate vehicle.

The compound minoxidil (6-amino-1,2-dihydro-1-hydroxy-2-imino-4-piperidinopyrimidine) was approved by the FDA for the treatment of male pattern baldness in August 1988. Minoxidil was recently approved by the FDA for the treatment of female androgenetic alopecia on August 13, 1991. The preparation of minoxidil is described in U.S. Patent Nos. 3,382,247, 3,644,364. Upjohn United States Patents (U.S. Patent Nos. 4,139,619 and

4,596,812) discloses the use of minoxidil in the topical treatment of human baldness. Similarly, an Upjohn United States Patent (U.S. Patent No. 5,026,691) discloses the use of minoxidil and an anti-inflammatory agent for the treatment of human baldness. Japanese patent Kokai 61-260010 states that topical minoxidil formulations containing other specified agents may be prepared.

It is also well known in the art that certain undesirable physiological manifestations, such as acne vulgaris, seborrhea, female hirsutism, and male pattern baldness and benign prostatic hypertrophy, are the result of hyperandrogenic stimulation caused by an excessive accumulation of testosterone or similar androgenic hormones in the metabolic system.

It is now known in the art that the principal mediator of androgenic activity in some target organs is 5α-dihydrotestosterone, and that it is formed locally in the target organ by the action of testosterone-5α-reductase. It is also known that inhibitors of testosterone-5α-reductase will serve to prevent or lessen symptoms of hyperandrogenic stimulation. For example, a number of 4-aza steroid compounds are known which are 5-alpha reductase inhibitors. See, for example, U.S. Pat. Nos. 2,227,876; 3,239,417; 3,264,301; and 3,285,918; French Pat. No. 1,465,544; Doorenbos and Solomons, J. Pharm. Sci. 62, 4, pp. 638-640 (1973); Doorenbos and Brown, J. Pharm. Sci., 60 8, pp. 1234-1235 (1971); and Doorenbos and Kim, J. Pharm. Sci. 63, 4, pp. 620-622 (1974).

In addition, U.S. Patents 4,377,584, 4,220,775, 4,859,681, 4,760,071 and the articles J. Med. Chem. 27, p. 1690-1701 (1984) and J. Med. Chem. 29, 2998-2315 (1986) of Rasmusson et al., U.S. Patent 4,845,104 to Carlin et al. and U.S. Patent 4,732,897 to Cainelli et al. describe 4-aza-17β-substituted-5α-androstan-3-ones which are said to be useful in the treatment of DHT-related hyperandrogenic conditions.

Further described in the field are the following two prior art references:

Proc. Natl. Acad. Sci, USA, Vol. 87, pp. 3640-3645, May 1990 by S. Andersson and D.W. Russell which describes structural and

biochemical properties of cloned and expressed human and rat steroid 5-alpha reductases; and

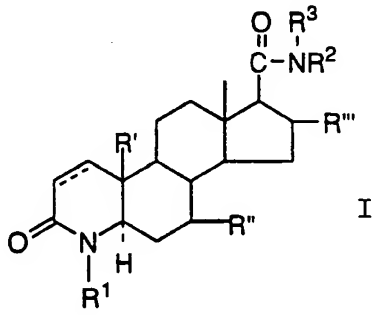
Nature, Vol. 354, Nov. 1991, pp. 159-161 by S. Andersson, et al., which describes the isolation of a second human enzyme, 5-alpha reductase 2, and the effect of a deletion in this gene in male pseudohermaphroditism.

The topical application of minoxidil has met with limited success. What is desired in the art is an improved formulation of minoxidil for treating patterned alopecia.

DESCRIPTION OF THE INVENTION

The present invention involves a method for treating patterned alopecia comprising the concomitant administration to a human host in need of such treatment of:

(A) a compound of the formula



I

wherein

the dotted line represents a double bond when present;

R^1 and R^3 are independently hydrogen, methyl or ethyl;

R^2 is a hydrocarbon radical selected from substituted or unsubstituted:

(a) straight or branched chain alkyl of from 1-12 carbons,

(b) cycloalkyl of from 3-12 carbons,

(c) -C_{1-3} alkyl-C_{3-12} cycloalkyl,

(d) aralkyl of from 7-12 carbons, such as e.g. benzyl, -CH_2CH_2-phenyl, and

(e) monocyclic aryl, such as e.g. phenyl,

with the proviso that R^2 is not t-butyl when R^1 and R^3 are H;

R' is hydrogen or methyl;

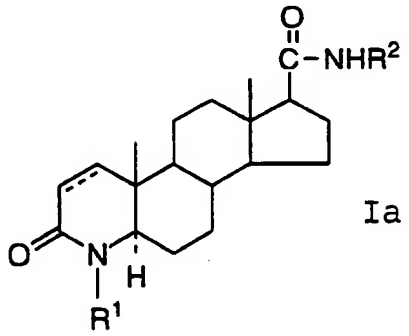
R" is hydrogen or β-methyl; and

R"' is hydrogen, α-methyl or β-methyl;

or a pharmaceutically acceptable salt or ester thereof, administered topically or orally; and

(B) minoxidil or a pharmaceutically acceptable salt thereof, administered topically.

In one embodiment of this invention, the compound of formula I applicable in the process of our invention is represented by the formula Ia:



Ia

wherein

the dotted line represents a double bond when present;

R^1 is hydrogen, methyl or ethyl; and

R^2 is selected from:

(a) branched chain alkyl of from 4-12 carbons (excluding t-butyl when R^1 is H),

(b) cycloalkyl of from 4-12 carbons,

(c) aralkyl of from 7-12 carbons,

(d) phenyl, unsubstituted or substituted by one or two of methyl, chloro or fluoro,

(e) substituted or unsubstituted 1- or 2-adamantyl, 1- or 2-adamantylmethyl, 1-, 2- or 7-norbornanyl, or 1-, 2- or 7-norbornanylmethyl;

or a pharmaceutically acceptable salt or ester thereof.

Representative compounds of the present invention include the following:

17β-(N-tert-amylcarbamoyl-4-aza-5α-androst-1-en-3-one,
17β-(N-tert-hexylcarbamoyl)-4-aza-5α-androst-1-en-3-one.
17β-(N-tert-butylcarbamoyl)-4-aza-4-methyl-5α-androst-1-en-3-one,
17β-(N-isobutylcarbamoyl)-4-aza-5α-androst-1-en-3-one,
17β-(N-tert-octylcarbamoyl)-4-aza-5α-androst-1-en-3-one,
17β-(N-octylcarbamoyl)-4-aza-5α-androst-1-en- 3-one, 17β-(N-1,1-diethylbutylcarbamoyl)-4-aza-5α-androst-1-en-3-one,.
17β-(N-neopentylcarbamoyl)-4-aza-5α-androst-1-en-3-one,
17β-(N-2-adamantylcarbamoyl)-4-aza-5α-androst-1-en-3-one,
17β-(N-1-adamantylcarbamoyl)-4-aza-5α-androst-1-en-3-one,
17β-(N-2-norbornylcarbamoyl)-4-aza-5α-androst-1-en-3-one,
17β-(N-1-norbornylcarbamoyl)-4-aza-5α-androst-1-en-3-one,
17β-(N-phenylcarbamoyl)-4-aza-4-methyl-5α-androst-1-en-3-one,
17β-(N-benzylcarbamoyl)-4-aza-4-methyl-5α-androst-1-en-3-one,
17β-(N-tert-amylcarbamoyl-4-aza-4-methyl-5α-androst-1-en-3-one,
17β-(N-tert-hexylcarbamoyl)-4-aza-4-methyl-5α-androst-1-en-3-one,
17β-(N-tert-butylcarbamoyl)-4-aza-4-methyl-5α-androst-1-en-3-one,
17β-(N-isobutylcarbamoyl)-4-aza-4-methyl-5α-androst-1-en-3-one,
17β-(N-tert-octylcarbamoyl)-4-aza-4-methyl-5α-androst-1-en-3-one,
17β-(N-1,1,3,3-tetramethylbutylcarbamoyl)-4-aza-5α-androst-1-en-3-one,
17β-(N-octylcarbamoyl)-4-aza-4-methyl-5α-androst-1-en-3-one,
17β-(N-1,1-diethylbutylcarbamoyl)-4-aza-4-methyl-5α-androst-1-en-3-one,
17β-(N-neopentylcarbamoyl)-4-aza-4-methyl-5α-androst-1-en-3-one,
17β(N-1-adamantylcarbamoyl)-4-aza-5α-androstan-3-one;

17β(N-1-adamantylcarbamoyl)-4-methyl-4-aza-5α-androst-1-en-3-one;
17β(N-1-adamantylcarbamoyl)-4-methyl-4-aza-5α-androstan-3-one;
17β-(N-1-adamantylmethylcarbamoyl)-4-aza-5α-androst-1-en-3-one;
17β-(N-2-adamantylcarbamoyl)-4-aza-5α-androstan- 3-one;
17β-(N-methyl-N-2-adamantylcarbamoyl)-4-methyl-4-aza-androstan-3-one;
17β-(N-2-adamantylcarbamoyl)-4-methyl-4-aza- 5α-androstane-3-one;
17β-(N-2-adamantylcarbamoyl)-4-methyl-4-aza-5α-androst-1-en-3-one;
17β-(N-methyl-N-2-adamantyl)carbamoyl-4-methyl-4-aza-androst-1-en-3-one;
17β-(N-(3-methyl)-1-adamantyl-carbamoyl)-4-aza-4-methyl-5α-androst-an-3-one;
17β-(N-exo-2-norbornanylcarbamoyl)-4-aza-4-methyl-5α-androst-1-en-3-one;
17β-(N-exo-2-norbornanylcarbamoyl)-4-aza-5α-androst-1-en-3-one;17β-(N-2-adamantylcarbamoyl)-4-aza-5α-androst-en-3-one;
17β-(N-methyl-N-2-adamantylcarbamoyl)-4-aza-4-methyl-androstan-3-one;
17β-(N-2-adamantylcarbamoyl)-4-methyl-4-aza-5α-androstan-3-one; and
17β-(N-methyl-N-2-adamantyl)carbamoyl-4-methyl-4-aza-androst-1-en-3-one.

Further examples of compounds useful in the present invention include the corresponding compounds of those above wherein the 4-aza substituent is substituted in each of the above named compounds with a hydrogen, methyl or an ethyl radical, to form a different N-substituent, and wherein a double bond can be optionally present as indicated by the dotted line in position 1 of formula I.

The alkyl, cycloalkyl, aralkyl, monocyclic aryl, 1- or 2-adamantyl or 1- or 2-norbornanyl moieties can be substituted with one or more substituents of the following: C_1-C_4 linear or branched alkyl, including methyl, ethyl, isopropyl, n-butyl; nitro; oxo; C_7-C_9 aralkyl, including benzyl; $(CH_2)_n$ COOR where n is 0, 1 or 2 and R is H or C_1-C_4 linear or branched alkyl including methyl, ethyl; CH_2OH; OH; OR^a

where R^a is C_1-C_4 linear or branched alkyl including methyl, ethyl; halo, including chloro, fluoro, bromo, iodo; COOH; $COOR^b$ where R^b is linear or branched C_1-C_4 alkyl; -$CONH_2$; CH_2NH_2; CH_2NHCOR^c where R^c is C_1-C_4 linear or branched alkyl including methyl, ethyl; phenyl; o, m, and p-substituted phenyl including p-nitro, p-amino and p-sulfo; or cyano. The amino group of the adamantyl or norbornanyl moiety can also be substituted as R^1 with methyl and ethyl, as well as hydrogen. The terms "norbornanyl" and "norbornyl" as used herein are intended to have the same meaning and may be used interchangeably in this application.

Also included within the scope of this invention are pharmaceutically acceptable salts or esters, where a basic or acidic group is present on the substituted alkyl, cycloalkyl, aralkyl, adamantyl or norbornanyl moiety. When an acidic substituent is present, i.e. -COOH, there can be formed the ammonium, sodium, potassium, calcium salt, and the like, for use as the dosage form.

Where a basic group is present, i.e. amino, acidic salts, i.e. hydrochloride, hydrobromide, acetate, pamoate, and the like, can be used as the dosage form.

Also, in the case of the -COOH group being present, pharmaceutically acceptable esters can be employed, e.g. acetate, maleate, pivaloyloxymethyl, and the like, and those esters known in the art for modifying solubility or hydrolysis characteristics for use as sustained release or prodrug formulations.

Representative examples include for R^2 (where AD is adamantyl):

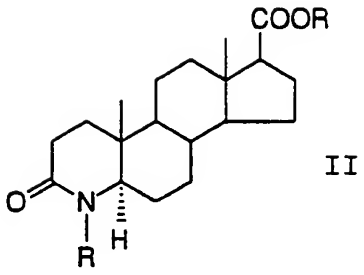
3, 5, 7-trinitro-1-AD; 4-oxo-1-AD; 1-benzyl-1-AD; 4,4-dimethyl-1-Ad; 3,7-dimethyl-5-carboxymethyl-1-AD; 3-carboxymethyl-1-AD; 3-chloro-1-AD; 1,3-dihydroxy-6,6-dimethyl-2-AD; 3-chloro-1-AD; 4-carbethoxy-2-AD; 4-carboxy-2-AD; 3-isopropyl-1-AD; 3-n-butyl-1-AD; 3-propyl-1-AD; 3-,5-diethyl-l-AD; 3-hydroxymethyl-1-AD; 2-carboxy-1-AD; 3-methyl-1-AD; 5-hydroxy-2-AD; 2-hydroxy-1-AD; 1-aminomethyl-1-hydroxy-2-AD; 2-oxo-1-AD; 2-phenyl-2-AD; 1-amino-methyl-2-AD; 1-carboxy-2-AD; 1-aminocarbonyl-2-AD; 3-hydroxy-

5,7-dimethyl-1-AD; 4-fluoro-1-AD; 3-fluoro-1-AD; 4-hydroxy-2-AD; 3-phenyl-1-AD; 3-(p-aminophenyl)-1-AD; 3-(p-nitrophenyl)-1-AD; 3-methyl-5-hydroxymethyl-1-AD; 3,5-dimethyl-4-hydroxy-1-AD; 2-hydroxymethyl-2-AD; 3-(p-sulfophenyl)-1-AD; 3-methyl-5-ethyl-1-AD; 2-carboxy-2-AD; 3,5-7-trimethyl-1-AD; 4-iodo-2-AD; 4-bromo-2-AD; 4-chloro-2-AD; 1-acetylaminomethyl-2-AD; 1-carboxymethyl-2-AD; 1-methyl-2-AD; 1-aminocarboxylmethyl-2-AD; 1-aminocarboxyl-1-AD; 2-cyano-2-AD; 3,5-dimethyl-7-ethyl-1-AD; 4-hydroxy-1-AD; 1-hydroxy-2-AD; 5-carboxy-3-methyl-1-AD; 3,5-dimethyl-7-carboxy-1-AD; 3-carboxy-1-AD; 3-hydroxy-1-AD; and the like.

Representative examples include for R^2 as substituted norbornanyl moieties are (where NB is norbornanyl): 2-NB; 1,7,7-trimethyl-4-phenyl-2-NB; 3-carboxy-2-NB; 3-phenyl-2-carboxy-2-NB; 2-cyano-3-phenyl-2-NB; 3-hydroxy-4,7,7-trimethyl-2-NB; 6-hydroxymethyl-2-NB; 5-cyano-2-NB; 3-allyl-2-NB; 1-NB; 7,7-dimethyl-1-hydroxymethyl-2-NB; 3-methoxy-4,7,7-trimethyl-2-NB; 3-aminocarbonyl-2-NB; 3-ethoxycarbonyl-2-NB; 3,3-dimethyl-2-NB; 7-oxo-1-NB; 3-phenyl-2-NB; 1-carboxy-methyl-7,7-dimethyl-2-NB; 1-ethyl-2-NB; 1-methyl-2-NB; 2,2,3,3,5,5,6,6,7,7-decafluoro-1-NB; 3-hydroxy-2-NB; 3-chloro-2-NB; 3-(p-methoxyphenyl)-2-NB; 2,2-dimethyl-3-methylene-7-NB; 3-oxo-2-NB; 1-methoxy-2-NB; 7-NB; 3-isopropyl-2-NB; 2-bromo-1-NB; 3-chloro-1-NB; and the like.

Procedures for preparing the compounds of Formula I useful in this invention, including the above, are well known in the art.

The novel compounds of formula I of the present invention can be prepared by a method starting with the known steroid ester (II) of the formula:



II

17β-(carbomethoxy)-4-aza-5-α-androstan-3-ones which includes the stages of optionally 1) dehydrogenating said starting material to produce the corresponding compound containing a double-bond in the 1,2-position of the A-ring, 2) converting the 17-carbomethoxy substituent into an N-substituted alkyl, cycloalkyl, aralkyl, monocyclic acyl, or adamantylcarbamoyl substituent and, if desired, 3) alkylating the A-ring nitrogen to introduce a N-methyl or N-ethyl substituent into the A ring 4-position. For the dehydrogenation step, it is preferable that the 4-aza nitrogen be unsubstituted. The alternate pathways can consist of one or more discrete chemical steps and if desired can take place before step (1) or following step (1) or step (3).

In accordance with the process of the present invention (see flow sheet), the products of our invention are formed by optionally: (1) heating a 17β-alkoxycarbonyl-4-aza-5α-androstan-3-ones, compound III, (prepared in the literature as described in the reference US Patent 4,377,584) with a dehydrogenating agent such as benzeneseleninic anhydride in a refluxing inert solvent, e.g. chlorobenzene, to form a 17β-alkoxycarbonyl-4-aza-5α-androst-1-ene-3-one IV (alternately, the dichlorodicyanobenzoquinone process of Dolling, et al., JACS 1988, Vol. 110, pp. 3318-3319, can be used); (2) the formed 5α-androst-1-en-3-one compound from Step 1 can be reacted with, e.g. sodium hydride under anhydrous conditions in a neutral solvent such as dimethyl-formamide; (3) contacting the resulting reaction mixture with an alkyl (methyl or ethyl) iodide to form the corresponding 17-β-alkoxy-adamantyl-carbamoyl-4-alkyl-4-aza-5α-androst-1-en-3-one V;

(4) subsequently hydrolyzing said 17β-alkoxycarbonyl-4-alkyl-4-aza-5α-androst-1-en-3-one with a strong base, such as aqueous methanolic potassium hydroxide at the reflux temperature, followed by acidification and isolation of the resulting steroidal acid to yield 17β-carboxy 4-alkyl-4-aza-5α-androst-1-en-3-one VI; (5) said steroidal acid can be then converted to its corresponding 2-pyridylthio ester by refluxing with triphenyl phosphine and 2,2'-dipyridyl disulfide in an inert solvent such as toluene and the resulting product 17β-(2-pyridylthiocarbonyl)-4-alkyl-4-aza-5α-androst-1-en-3-one VII can be isolated by chromatography on e.g. silica gel; and (6) said pyridylthio ester can be then reacted with 1-adamantyl-, 2-adamantylamine or norbornanylamine in an inert solvent e.g. tetrahydrofuran, to form the desired product 17β-N-adamantylcarbamoyl-4-alkyl-4-aza-5α-androst-1-en-3-one VIII which can be isolated by chromatography e.g. on silica gel. When the previous reaction is carried out in the absence of first forming the double bond at position 1, the corresponding 17β-(N-adamantylcarbamoyl)-4-alkyl-4-aza-5α-androstan-3-one (or N-norbornanyl carbamoyl compound) is prepared.

In accordance with an alternate process of our invention the corresponding N-unsubstituted-17β(N-adamantyl-carbamoyl)-4-aza-5α-androst-1-en-3-one XIV is readily prepared from the 17β (alkoxycarbonyl)-4-aza-5α-androstane-3-one IV by repeating the above series of reaction steps but omitting the alkylation Step 2 herein above, i.e. treatment of the 4-aza-5α-androst-1-en-3-one with e.g. sodium amide followed by methyl or ethyl iodide via intermediates XII and XIII.

In accordance with a further alternate process of preparing the compounds of our invention having only hydrogen as the sole substituent on the ring A - nitrogen, the double bond in the A ring is introduced as the last step of the process. Thus, a 17β-alkoxycarbonyl-4-aza-5α-androstan-3-one III is hydrolyzed to the corresponding steroidal acid IX 17β-carboxy-4-aza-5α-androstan-3-one which in turn is converted to the corresponding pyridylthio ester, 17β (2-pyridylthiocarbonyl)-4-aza-5α-androstan-3-one, X followed by treatment of the ester with an amine of formula R^2-NH_2 wherein R^2 is as defined

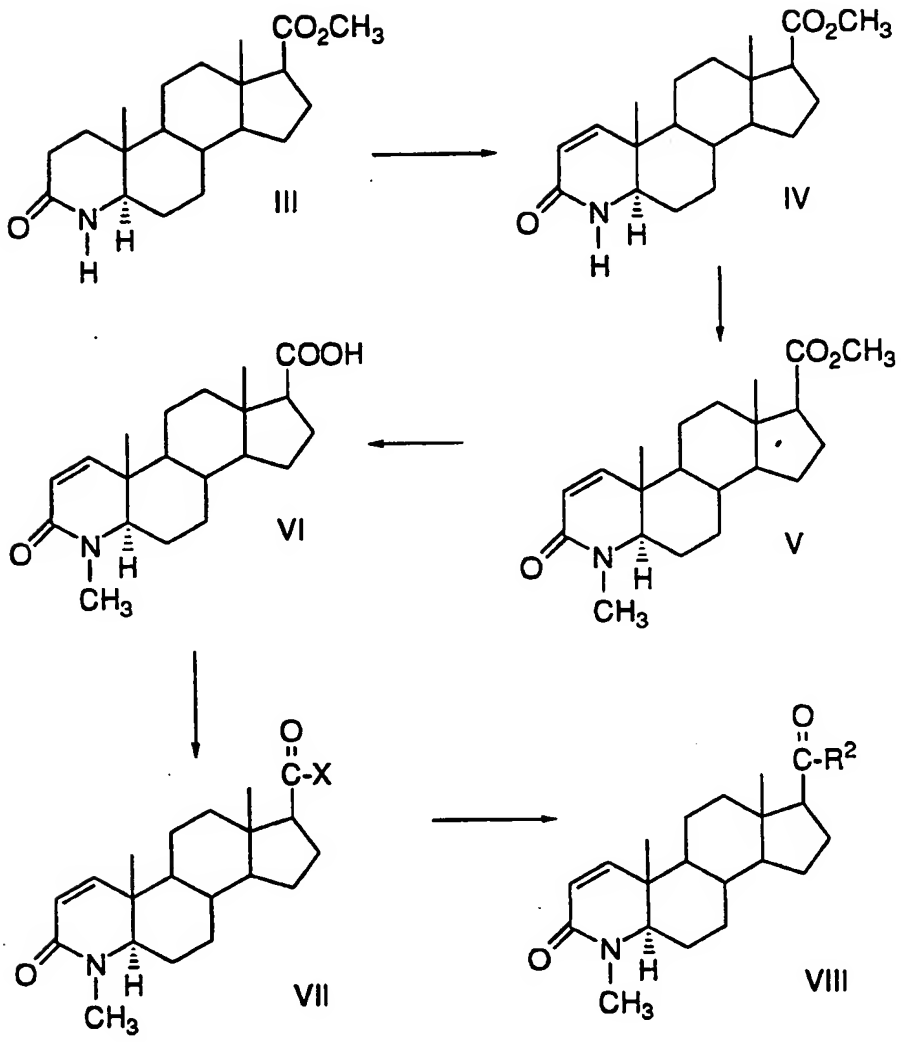
hereinabove as 1- or 2-adamantyl or 1-, 2-, or 7-norbornanyl to form a 17β (N-adamantyl-carbamoyl)-4-aza-5α-androstane-3-one XI which is dehydrogenated as previously described to produce compound XIV, 17β-(N-adamantyl-carbamoyl)-4-aza-androst-1-en-3-one or corresponding norbornanyl derivative.

In another alternate method of introducing the 17β-(N-adamantyl-carbamoyl)substituent into a 17β-carboxy androstane compound of formula VI, XII or IX, each is treated in a manner similar to the procedure described in Steroids, Vol. 35 #3, March 1980, p. 1-7 with dicyclohexylcarbodiimide and 1-hydroxybenzo-triazole to form the 17β-(1-benzotriazoloxycarbonyl)-4-aza-5α-androst-1-en-3-one, VII, XIII or compound X, wherein the substituent X is benzotriazoloxy group.

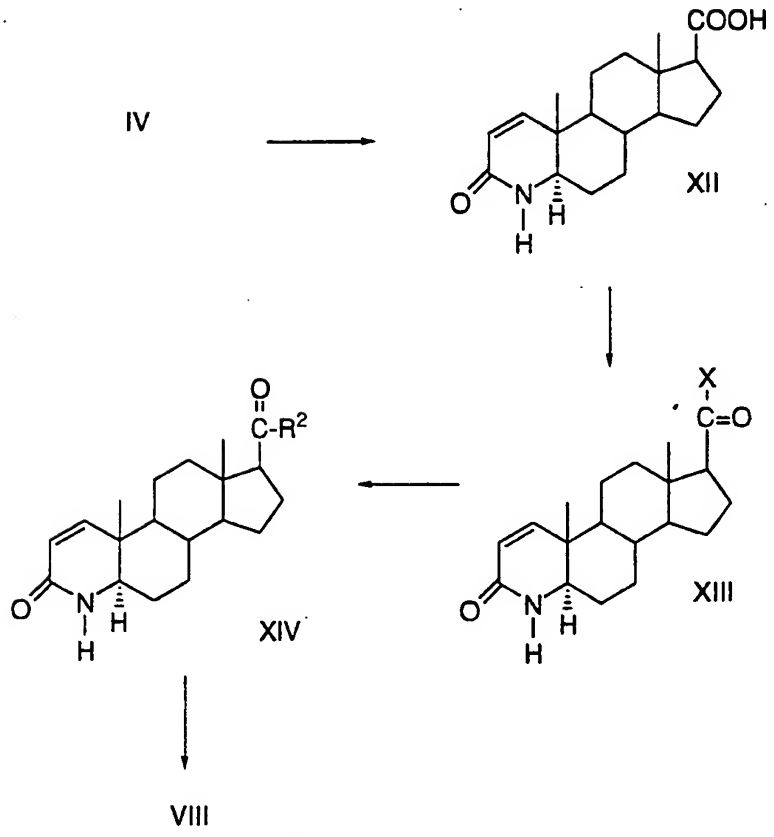
The 16-methyl derivative wherein R''' is methyl are prepared from known 16-methyl-17-acyl-4-methyl-4-aza-5α-androstan-3-ones, e.g. 4,16β-dimethyl-17β-acetyl-4-aza-5α-androstan-3-one by known dehydrogenation procedures for 4-methyl-4-aza compounds to produce the corresponding 4,16β-dimethyl-17β-acetyl-4-aza-5α-androst-1-en-3-one.

The above reactions are schematically represented in the following flowsheet.

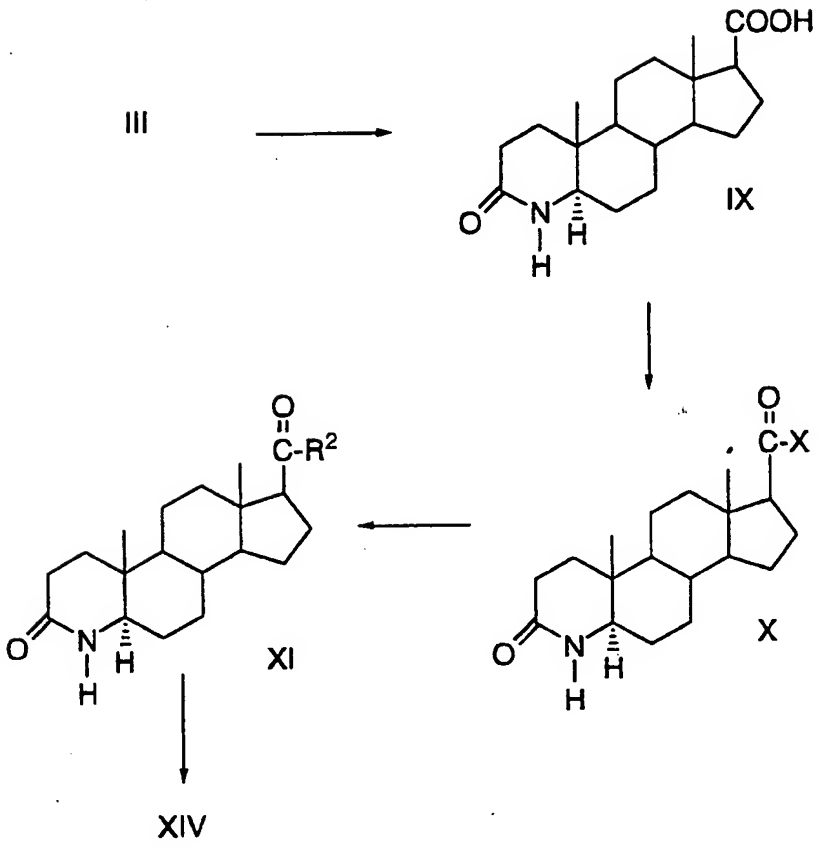
Flowsheet



Flowsheet-continued



Flowsheet-continued



X is 2-pyridylthio or 1-benzotriazoloxy.
R^2 is 1- or 2-adamantyl or norbornanyl.

The compounds of the present invention, prepared in accordance with the method described above, are, as already described, potent and selective antiandrogens in the treatment of patterned alopecia by virtue of their ability to specifically inhibit testosterone-5α-reductase.

The compounds of Formula I may be employed in a pharmaceutical composition additionally comprising a potassium channel opener, such as one selected from the group consisting of minoxidil, cromakalim, pinacidil, a compound selected from the classes of s-triazine, thiane-1-oxide, benzopyran, or pyridinopyran derivatives, or a pharmaceutically acceptable salt thereof. Particularly, the compounds of Formula I may be employed in a pharmaceutical composition additionally comprising minoxidil or a pharmaceutically acceptable salt thereof. The compositions are useful in hair revitalizing, such as in the treatment of male pattern alopecia, female pattern alopecia, alopecia senilis or alopecia areata, by providing epilation prevention, hair germination, and/or a promotion of hair generation and hair growth.

The compound of formula I may be administered topically, parenterally or systemically, including orally, while the potassium channel opener, e.g., minoxidil, is administered topically, in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In particular, modes of administration include topical administration of minoxidil in combination with oral or topical administration of a compound of Formula I.

The present invention is thus also concerned with providing suitable topical and systemic pharmaceutical formulations for use in the novel methods of treatment of the present invention. The active agents can be administered in a single topical pharmaceutical formulation, or each active agent can be administered in a separate pharmaceutical formulation, e.g., in separate topical

pharmaceutical formulations, or e.g., an oral pharmaceutical formulation of a compound of formula I in combination with a topical pharmaceutical formulation of, e.g., minoxidil. See, e.g., U.S. Patent No.'s 4,596,812, 4,139,619 and WO 92/02225, published 20 February 1992, for dosages and formulations of potassium channel openers. For combination treatment where the active agents are in separate dosage formulations, the active agents can be administered concomitantly, or they each can be administered at separately staggered times. For example, a compound of Formula I may be administered prior to, concurrent with, or subsequent to the topical administration of minoxidil.

The pharmaceutical compositions of this invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains one or more of the compounds of the present invention as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for oral, external, enteral or parenteral applications. The active ingredient may be compounded, for example, with the usual non- toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. Topical pharmaceutical compositions may be, e.g., in the form of a solution, cream, ointment, gel, lotion, shampoo or a formulation suitable for spraying onto the skin such as an aerosol formulation. For example, the compounds of Formula I and minoxidil may be utilized with hydroxypropyl methyl-cellulose essentially as described in U.S Patent No. 4,916,138, issued April 10, 1990, or with a surfactant essentially as described in EPO Publication 0.428.169. Dosage forms for external application may be prepared essentially as described in EPO Publication 0.423.714 or in U.S. Patent

No. 4,938,953. The active object compounds are included in the pharmaceutical composition in a therapeutically effective amount, that is, an amount sufficient to produce the desired effect upon the process or condition of diseases.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For external administration the compound of Formula I may be formulated within the range of, for example, 0.0001% to 60% by weight, preferably from 0.001% to 10% by weight, and most preferably from about 0.005% to 0.8% by weight. In general, the dose of the compound of Formula I for a human being is preferably 1 to 2000 mg, more preferably 1 to 20 mg, per day per person,

For external administration, minoxidil may be formulated in the composition within the range of, for example, 0.1% to 10.0% by weight, and preferably from 1% to 5% by weight.

In addition, the compositions of the present invention may be administered on an intermittent basis; i.e. at semidaily, daily, semiweekly, weekly, semi-monthly or monthly intervals.

It will be understood, however, that the specific dose level for any particular patient will depend on a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The following examples are given for the purpose of illustrating the present invention and shall not be construed as being limitations on the scope or spirit of the instant invention.

EXAMPLE A

A lotion comprising the composition shown below may be prepared.

Ingredient	(weight %)

95% Ethanol	80.0
Compound of Formula I	3.0
Minoxidil	2.0
α-Tocopheral acetate	0.01
Ethylene oxide (40 mole) adducts of hardened castor oil	0.5
Purified water	14.0
perfume and dye	q.s.

Into 95% ethanol are added a compound of Formula I, minoxidil, α-tocopherol acetate, ethylene oxide (40 mole) adducts of hardened castor oil, perfume, and a dye, and the mixture is stirred and dissolved, followed by an addition of purified water, to obtain a liquid lotion.

EXAMPLE B

An emulsion is prepared from A phase and B phase having the following compositions.

(A phase)	(weight %)
Whale wax	0.5
Cetanol	2.0
Petrolatum	5.0
Squalane	10.0
Polyoxyethylene (10 mole) monostearate	2.0
Sorbitane monooleate	1.0
Compound of Formula I	0.01
Minoxidil	0.5

(B phase)	(weight %)
Glycerine	10.0
Purified water	68.5
Perfume, dye, and preservative	q.s.

The A phase and the B phase are respectively heated and melted and maintained at 80°C, both phases are mixed to be emulsified, and are cooled under stirring to normal temperature to obtain an emulsion.

EXAMPLE C

A cream is prepared from A phase and B phase having the following compositions.

(A phase)	(weight %)
Fluid paraffin	5.0
Cetostearyl alcohol	5.5
Petrolatum	5.5
Glycerine monostearate	3.0
Polyoxyethylene (20 mole) 2-octyldodecyl ether	3.0
Propylparaben	0.3

(B phase)	(weight %)
Compound of Formula I	0.8
Minoxidil	1.0
Glycerine	7.0
Dipropylene glycol	20.0
Polyethylene glycol 4000	5.0
Sodium Hexametaphosphate	0.005
Purified water	43.895

The A phase is heated and melted, and maintained at 70°C, the B phase is added to the A phase followed by stirring, and the obtained emulsion is cooled to obtain a cream.

EXAMPLE D

A hair liquid comprising the composition shown below may be prepared.

Ingredient	(weight %)
Polyoxyethlene butyl ether	20.0
Ethanol	50.0
Compound of Formula I	1.0
Minoxidil	1.0
Propylene glycol	5.0
Polyoxyethylene hardened castor oil derivative (ethylene oxide 80 mole adducts)	0.4
Perfume	q.s.
Purified water	q.s.

Into ethanol is added polyoxypropylene butyl ether, propylene glycol, polyoxyethylene hardened castor oil, a compound of

Formula I, minoxidil, and perfume, which are mixed under stirring, and to the mixture is added purified water, to obtain a hair liquid.

EXAMPLE E

A hair shampoo comprising the composition shown below may be prepared.

Ingredient	(weight %)
Sodium laurylsulfate	5.0
Triethanolamine laurylsulfate	5.0
Betaine lauryldimethylaminoacetate	6.0
Ethylene glycol distearate	2.0
Propylene glycol	5.0
Compound of Formula I	1.0
Minoxidil	2.0
Ethanol	2.0
Perfume	0.3
Purified water	71.7

Into 71.1 g of purified water is added 5.0 g of sodium laurylsulfate, 5.0 g of triethanolamine laurylsulfate, 6.0 g of betaine lauryldimethylaminoacetate, then a mixture obtained by adding 1.0 g of a compound of Formula I, 2.0 g of minoxidil, 5.0 g of polyethylene glycol, and 2.0g of ethylene glycol distearate to 2.0 g of ethanol, followed by stirring, and 0.3 g of perfume, is successively added, and the mixture is heated then cooled to obtain a hair shampoo.

Accordingly, the present invention is also particularly concerned with providing a method of treating patterned baldness in human males and females by topical, systemic or oral administration by concomitant therapy of the compounds of the present invention.

The present invention is thus also concerned with providing suitable topical and systemic pharmaceutical formulations for use in the novel methods of treatment of the present invention.

The compositions containing the compounds of the present invention as the active ingredient for use in the treatment of patterned baldness can be administered in a wide variety of therapeutic dosage forms in conventional vehicles for systemic administration, as, for example, by oral administration in the form of tablets, capsules, solutions, or suspensions, of by intravenous injection. The compositions are preferably provided in the form of scored tablets containing 0.1, 1, 5, 10, 25, 50, 100, 150, 250, and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.01 mg. to about 50 mg./kg. of body weight per day. Preferably the range is from about 0.02 mg. to 75 mg./kgs. of body weight per day. This translates to a dosage of about 1 to 2000 mg/day and preferably 1 to 20 mg/day per person. Administration is preferred 1-3 times/day per person. Capsules containing the product of this invention can be prepared by mixing an active compound of the present invention with lactose and magnesium stearate, calcium stearate, starch, talc, or other carriers, and placing the mixture in gelatin capsule. Tablets may be prepared by mixing the active ingredient with conventional tableting ingredients such as calcium phosphate, lactose, corn starch or magnesium stearate. The liquid forms in suitably flavored suspending or dispersing agents such as the synthetic and natural gums, for example, tragacanth, acacia, methylcellulose and the like. Other dispersing agents which may be employed include glycerin and the like. For parenteral administration, sterile suspensions and solutions are desired. Isotonic preparations which generally contain suitable preservative are employed when intravenous administration is desired.

Preferably, the compound of formula I is administered orally and the minoxidil administered topically as a cream or lotion.

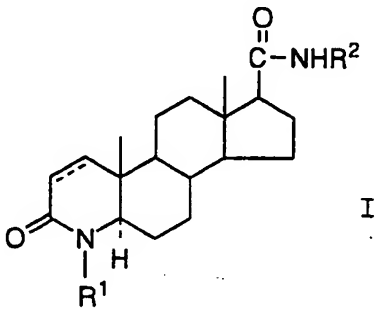
The method of preparing the compounds involved in the present invention, already described above in general terms, may be further illustrated by the following examples.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the casual variations, adaptations, modifications, deletions, or additions of procedures and protocols described herein, as come within the scope of the following claims and its equivalents.

EXAMPLE 1

Methyl 3-oxo-4-aza-5α-androst-1-ene-17β-carboxylate

A suspension of 83.7 g of methyl 3-oxo-4-aza-5α-androstane-17-carboxylate* and 126.5 g of benzeneseleninic anhydride in 2.09 l of chlorobenzene was heated at reflux for 2 hours. The reflux condenser was switched to a distillation head and the mixture was distilled slowly to remove water that had formed in the reaction (2 hours). The solution was evaporated to leave 198 g of wet residue. The residue as a solution in dichloromethane was washed with saturated aqueous $NaHCO_3$ solution and saturated NaCl solution, then dried and evaporated to leave 172.4 g. This material was chromatographed on 2.56 kg of silica gel eluting first with dichloromethane (5 l) and then with 4:1 dichloromethane acetone. The desired product eluted after 8 l and amounted to 53:4 g. It was rinsed with diethyl ether and dried to leave 49.5 g, of the title compound m.p. 278-280°C. In a similar fashion the following compounds were converted to their corresponding 1,2-unsaturated derivatives:



II

		m.p.
1a	R = $CONHC(CH_3)_3$	252-254°C
1b	= $CONHC(CH_3)_2CH_2C(CH_3)_3$	224-226°

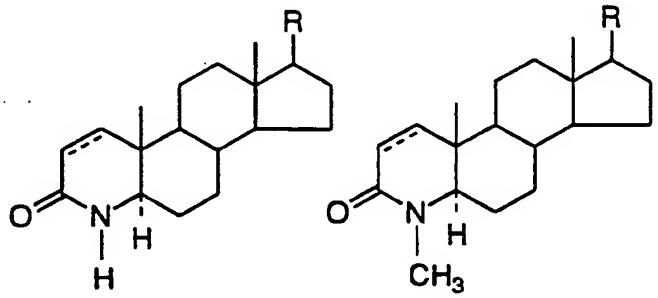
* Rasmusson Johnston and Arth.
U.S. Patent 4,377,584, March 22, 1983.

EXAMPLE 2

Methyl 4-methyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxylate

A suspension of 25 g of the product of Example 1 and 2.25 g of sodium hydride in 500 ml of dry dimethylformamide was stirred under nitrogen for 15 minutes. Methyl iodide (15 ml) was added dropwise and the mixture was stirred for 30 minutes at room temperature. Additional (5 ml) methyl iodide was added and the mixture was heated at 50°C for 2 hours. After cooling the mixture was diluted with water to a volume of 2 liters. The solid was separated after cooling and amounted to 25.4 g, m.p. 159-161°C.

In a similar fashion the following compounds were converted to their corresponding 4-methyl derivatives:



		m.p.
2a	R = $CONHC(CH_3)_2CH_2C(CH_3)_3$, androstane	148-150°C
2b	= CONHC(CH3)3; Δ-1-androstene	153-155°
2c	= $CONHC(CH_3)_2CH_2C(CH_3)_3$ Δ-1-androstene	168-170°

EXAMPLE 3

S-(2-Pyridyl) 4-methyl-3-oxo-4-aza-5α-androst-1-ene-17β-thiocarboxylate

A suspension of 25 g of the product of Example 2 in 125 ml of methanol was treated with a solution of KOH (*12.5 g) in 12.5 ml of water. After refluxing for 4 hours, the solution was acidified with 6 NHCl and then was diluted with water. The crude acid (23.32 g) was separated, dried and had m.p. 300°C.

The crude, dry acid (23 g), triphenylphosphine (36.45 g) and 2,2'-dipyridyldisulfide (30.4 g) were suspended in 138 ml of toluene with stirring for 3 hours at room temperature. The reaction mixture was directly chromatographed on a column of 4.5 kg of silica gel eluting with 9:1 ethyl acetate-acetone to give 20.4 g of the desired product, m.p. 218-220°C.

Continued elution with acetone gave 5.2g of the methanol addition product, S-(2-pyridyl) 1a-methoxy-4-methyl-3-oxo-4-aza-5α-androstane-17β-thiocarboxylate, m.p. 221-223°C as a by-product.

3A. In a similar fashion the product of Example 1 was converted into S-(2-pyridyl) 3-oxo-4-aza-5α-androst-1-ene-17β-thiocarboxylate, m.p. 230-232°C.

3B. In a similar manner methyl 3-oxo-4-aza-5α-androstane 17-carboxylate was converted into S-(2-pyridyl) 3-oxo-4-aza-5α-androstane-17β-thiocarboxylate, m.p. 232-234°C.

EXAMPLE 4

N-t-butyl 4-methyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide

Anhydrous t-butylamine was added to a suspension of 2.5 g of the pyridylthioester of Example 3 in 70 ml of tetrahydrofuran. After 60 minutes exposure, the resulting solution was evaporated and the residue was chromatographed on 125 g of silica gel. Elution with

20:1 ethyl acetate dichloromethane afforded 1.5 g of the product, m.p. 152-154°C.

When the example is repeated using an appropriate amine and an appropriate pyridylthioester, the following products were obtained:

4b: N-t-butyl 3-oxo-4-aza-5α-androstane-17β-carboxamide, m.p. 275-276°C.

4c: N-(2,4,4-trimethyl-2-pentyl)4-methyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide, m.p. 168-170°C.

EXAMPLE 5

5-Oxo-3,5-secoetian-3,20-dioic acid

To a solution of 200 g of 3-oxo-4-etien-17β-oic acid in 3.5 l of t-butanol at 80° was added a solution of 198.4 g of sodium carbonate in 474 ml of water. A warm (65°C) solution of 948.5 g of sodium metaperiodate and 6.95 g of permanganate in 3.5 l of water was added at such a rate that the reaction mixture was maintained at 80°C. After addition the mixture was heated at reflux for one hour. The mixture stood at room temperature overnight. The inorganic salts were removed by filtration and the cake was washed with 225 ml of water. A solution of 5% aqueous sodium bisulfite was added to reduce the iodine that was present. The T-butanol was removed under reduced pressure and the aqueous residue was acidified with conc. hydrochloric acid. The separated gum was extracted into dichloromethane and was washed with 5% aqueous sodium bisulfite, saturated sodium chloride solution, then dried and concentrated to an off-white residue (214 g). Crystalline material was obtained by suspending the residue in ether and diluting with hexane to give 152 g, m.p. 189-192°C.

EXAMPLE 5B

3-Oxo-4-aza-5-etien-20-oic acid

A suspension of 64.7 g of the dioic acid of Step 5 in 350 ml of ethylene glycol was treated with 80 ml of liquid ammonia. The resulting solution was heated at a rate of 3°/min. up to 180°C and was held at that temperature for 15 minutes. After cooling, 1 liter of water was added and the mixture was acidified with 10% hydrochloric acid to a pH of 1.5. The product was removed and washed with water, then air dried to leave 57.5 g of the product, m.p. 310°C.

EXAMPLE 5C

3-Oxo-4-aza-5α-etian-20-oic acid

A solution of 136 g of the 5-acid of Example 5B in 16.32 ml of acetic acid was hydrogenated at 60°C in the presence of platinum catalyst (from 16.32 g of PtO_2) at 40 psig for 3 hours. The catalyst was removed and the solution concentrated to give 128.2 g of crude product. The material was washed well with 3 l of water then filtered an air dried to leave 125 g of the white solid, m.p. 310°.

This material is also obtained by saponification of methyl 3-oxo-4-aza-5α-androstane-17β-carboxylate (methyl 3-oxo-4-aza-5α-etien-17β-oate) in 7% methanolic potassium hydroxide followed by an acidic work-up.

EXAMPLE 5D

N-(2,4,4-trimethyl-2-pentyl)3-oxo-4-aza-5α-androstane-17β-carboxamide

A solution of 5.0 g of the product of Example 5C, 3.35 g of dicyclohexylcarbodiimide and 3.18 g of 1-hydroxybenztriazole in 500 ml of dichloromethane was stirred at room temperature overnight.

The solid was separated by filtration and the filtrate was treated with 2,4,4-trimethyl-2-pentylamine (t-octylamine). This solution stood at room temperature for 64 hours. A small amount of solid was removed and the solution was washed successively with 10% aqueous sodium hydroxide, water, 10% hydrochloric acid and saturated aqueous sodium chloride. After drying and concentration the crude product was eluted through 240 g of silica gel with 3:7 acetone-dichloromethane to give 5.5 g of the product, m.p. 250-251°C.

EXAMPLE 5E

Example 5D is repeated using t-butylamine in place of 2,2,4-trimethyl-2-pentylamine to obtain N-t-butyl 3-oxo-4-aza-5α-androstane-17β-carboxamide, m.p. 274-276°C.

EXAMPLE 6

Synthesis of 17β(N-1-adamantyl-carbamoyl)-4-aza-5α-androst-1-en-3-one

100 mg of the 17-methyl ester (0.305 mmoles) from Example 1 was suspended in 3.0 ml of THF (dried over molecular sieves 3A), and then was added 183.0 mg of 1-adamantanamine (1.2 mmoles). The suspension was cooled to 5-10°C and then 590 µl of 2.0 M solution, of EtMgBr in THF was added. The resulting mixture was allowed to stir for 10 minutes, and then refluxed for 1-2 hours under N_2. The mixture was cooled to 0°C and then quenched with saturated solution of NH_4Cl (about 10 ml.). The organic layer was separated and the aqueous layer extracted with three volumes CH_2Cl_2.

The organic layers were combined, washed 2 times with H_2O, twice with saturated sodium chloride, and dried over $MgSO_4$, filtered and evaporated to dryness in vacuum. Crystallization from EtOAc afforded 75.0 mg of product. Recrystallization from MeOH and drying at 110°C for 2 hours/0.1 mm gave product, mpt. 305-306°C. Molecular weight (by FAB) showed M^+=451: Calculated =451.

Anal. Calcd. for $C_{29}H_{42}N_2O_2$:
C, 77.28; H, 9.40; N, 6.21.
Found: C, 76.84; H, 9.73; N, 5.93.

EXAMPLE 7

Synthesis of 17β(N-2-adamantyl-carbamoyl)-4-aza-5α-androst-1-en-3-one

Following the above-described general procedure of Example 6 but utilizing 2-adamantamine (prepared by aqueous neutralization of the hydrochloride and EtOAc extraction and isolation) in place of 1-adamantamine, and carrying out the reflux for 7 hours rather than 1-2 hours, the title compound is prepared, mpt. 284-285°C.

EXAMPLE 8

Synthesis of 17β(N-1-adamantylcarbamoyl)-4-aza-5α-androstane-3-one

100.0 mg of the adamantyl derivative produced in Example 6 was dissolved in 5.0 ml of dry THF. 300 mg of 5% Pd/C was added and the mixture was hydrogenated for 6.0 hrs. at R.T. at 40 psi. The mixture was filtered through celite, the cake washed with THF (3 times) and solvent evaporated under vacuum to yield 97.0 mg. of crude above-titled product. NMR showed absence of olefins. The crude material was placed on 15.0 g silica gel column, and eluated with 1:1(CH_2Cl_2: acetone).

Collected fractions afforded a single spot material by TLC weighing 77.98 mg. NMR was in excellent agreement with the proposed structure. Recrystallized from EtOAc to yield 65.59 mg of the above-titled product, mp. 323-324°C.

Anal. Calcd. for $C_{29}H_{44}O_2N_2$ 1/4 H_2O:
C, 76.18; H, 9.81; N, 6.13.
Found: C, 75.91; H, 9.97; N, 6.06.

EXAMPLE 9

Synthesis of 17β(N-1-adamantylcarbamoyl)-4-methyl-4-aza-5α-androst-1-en-3-one

120 mg of the thiopyridyl ester of Example 3 was suspended in 20 ml of dry THF, to the suspension was added 175.0 mg of 1-adamantanamine under N_2. The reaction was carried out at R.T. for 16 hours under N_2. The reaction was monitored by silica gel TLC, using 1:1 acetone: hexane. The product was separated on TLC 20 cm x 20 cm, 1000 μm silica gel plate, eluted with 1:1 (acetone/hexane). The product was crystallized from ethyl acetate, to give 50.0 mg of pure material m. pt. 202-205°C. Molecular Weight (FAB) showed 465; Calc: 465. Recrystallization afforded 19.14 mg of the above-titled product, m.pt. 202-202.5°C.

Anal. Calcd for $C_{30}H_{44}N_2O_2 \cdot H_2O$:
C, 74.64; H, 9.60; N, 5.80.
Found: C, 74.32; H, 9.47; N, 5.89.

EXAMPLE 10

Hydrolysis of Methyl-3-oxo-4-aza-5α-androstane-17β-carboxylate

The 17β-androstane carboxylate starting material of Example 1 was hydrolyzed with 7% KOH in isopropanol or aqueous methanol, followed by an acidic work-up to give the corresponding 17β carboxylic acid which was utilized in Example 11.

EXAMPLE 11

N-(1-adamantyl)-3-oxo-4-aza-5α-androstane-17β-carboxamide

A solution of 5.0 g of the product of Example10, 3.35 g of dicyclohexylcarbodiimide and 3.18 g of 1-hydroxybenztriazole in 500 ml of dichloromethane was stirred at room temperature overnight. The solid was separated by filtration and the filtrate was treated with 1-

adamantamine. This solution stood at room temperature for 64 hours, then filtered, and the solution was washed successively with 10% hydrochloric acid and saturated aqueous sodium chloride. After drying with $MgSO_4$, it was filtered and concentrated. The crude product was eluted through 240 g of silica gel with 3:7 (acetone-dichloromethane) to give 5.5 g of the above-titled product, m.p. 323-324°C.

EXAMPLE 12

Synthesis of Benztriazol-1-yl-3-oxo-4-methyl-4-aza-5α-androstan-17β-carboxylate

A suspension of 83.7 g of methyl-3-oxo-4-methyl-4-aza-5α-androstane-17β-carboxylate. (See Rasmusson, et al. J. Med. Chem 29, 2298-2315, 1986) was hydrolyzed with 7% KOH in aqueous methanol, followed by an acidic work up to give the corresponding 17β-carboxylic acid.

The acid was readily converted into benzotriazyl-1-yl-3-oxo-4 methyl-4-aza-5α-androstane-17β-carboxylate as described in Example 13. The activated ester (the benzotriazoyl derivative) was purified on TLC (4 plates, 20 cm x 20 cm x 20 cm x 1000μm silica gel) eluted with 4:96 (MeOH-$CHCl_3$). The isolated product was washed with ether to give the active ester m.pt. 198-200°C with decomposition.

EXAMPLE 13

Synthesis of 17β (N-1-adamantylcarbamoyl)-4-methyl-4-aza-5α-androstan-3-one

100.0 mg of the 4-methyl-4-aza-benzotriazole derivative prepared as described in Example 12, was dissolved in 20.0 ml CH_2Cl_2. To the clear solution was added 127 mg of 1-adamantamine. The reaction mixture was stirred overnight at R.T./N_2.

Crystallization from EtOAc after filtering the solution through Teflon Acrodisc CR afforded 26.32 mg, m.pt. 210-217°C. The product was further purified on 1.0 g silica gel column (EM silica gel)

with 1:1 (acetone-hexane) as eluant to give after recrystallization (ethyl acetate) 21.75 mg of white needles of the above-titled product, m.pt. 203-205°C.

Anal. Calcd. for $C_{30}H_{46}N_2O_2 \cdot 1.5\ H_2O$:
C, 73.58; H, 9.68; N, 5.62;
Found: C, 73.15; H, 9.30; N, 5.67.

EXAMPLE 14

Diastereomeric Synthesis of 17β(N-exo-2-norbornanyl-carbamoyl)-4-aza-5α-androst-1-en-3-one)

100.0 mg of the corresponding 4-H thiopyridylester of Example 3, prepared by the procedure of Example 3, but utilizing the 4-H methyl ester product of Example 1, (See Rasmusson et al. J. Med. Chem. Vol. 29, pp. 2298-2315 (1986), was dissolved in 3.0 ml of dry THF under N_2. To the clear solution was added 477 µl of (±) racemic exo-2-aminonorbornane. Allowed the reaction to proceed for 16 hours at R.T./N_2. The reaction mixture was evaporated to dryness in vacuum. The residue was dissolved in chloroform. The organic layer was washed with 2.5 N HCl acid (3 times); 3 times with water; 3 times with saturated NaCl solution, dried over $MgSO_4$, filtered and evaporated to dryness in vacuum to afford 56.3 mg of a racemic diastereomeric mixture.

The crude product was chromatographed on TLC (2 plates, 20 cm x 20 cm x 500 µm silica gel) eluted with 70:30 ($CHCl_3$:acetone) to yield 43.4 mg.of the above-titled product. Recrystallization from EtOAc yielded 30 mg product, m.pt 245-245.9°C.

NMR ($CDCl_3$) confirmed the above structure.

FAB mass spectrum calcd. for $C_{26}H_{38}O_2N_2$: m/e 411; Found: 411.

Anal. Calcd. for $C_{26}H_{38}O_2N_2.H_2O$:
C, 72.82; H, 9.40; N, 6.58.
Found: C, 73.21; H, 9.20; N, 6.25.

EXAMPLE 15

Synthesis of 17β(N-1-adamantylmethylcarbamoyl)-4-aza-5α-androst-1-en-3-one

200.0 mg of the 4-H thiopyridyl aza steroid, used in Example 14, was suspended in 2.0 ml of dry THF.

To the suspension was added 400 µl of 1-aminomethylene adamantane via syringe at R.T./N_2. After several minutes, a yellow clear solution resulted and after 1/2 hr., precipitation occurred. The reaction was allowed to proceed overnight/N_2. Diluted with CH_2Cl_2, washed with 10% NaOH, two times, then with H_2O two times, followed by 10% HCl (two times), H_2O (two times), and finally two times with satd. NaCl solution.

The organic layer was dried over $MgSO_4$, filtered, concentrated in vacuo to obtain the product, as shown by NMR, recrystallized from EtOAc, to yield 149.0 mg product, m.pt 255-257°C with decomposition.

FAB Mass Spectrum, Calcd: m/e 464 + 1 = 465:
Found 465.

EXAMPLE 16

Synthesis of 17β(N-2-adamantylcarbamoyl)-4-aza-5α-androstan-3-one

A mixture of 1.09 grams 17β-(N-2-adamantylcarbamoyl)-4-aza-5α-androst-1-en-3-one (See Example 10 for preparation), 150 ml of ethanol, and 1.0 g. of 30% Pd/C was hydrogenated overnight with shaking under 45 psig. hydrogen pressure. The suspension was filtered to remove catalyst, and evaporated to dryness to yield a grey residue. This was chromatographed by elution on a 200 ml silica gel column with 40:60 acetone/methylene chloride eluant to yield 1.0 g of solid, mp. 294-296°C.

Anal. Calcd. for $C_{29}H_{44}N_2O_2 \cdot 0.2H_2O$

Calcd. C, 76.33; H, 9.80; N, 6.14

Found C, 76.23; H, 9.86; N, 5.92

Mass Spec. Analysis by electron impact showed MW of 452.

EXAMPLE 17

Synthesis of 17β-(N-2-adamantylcarbamoyl)-4-aza-4-methyl-5α-androst-1-en-3-one

A suspension of 500 mg of 17β-(N-2-adamantylcarbamoyl)-4-aza-5α-androst-1-en-3-one, as prepared in Example 16, 10 ml sieve-dried DMF, 140 mg NaH, were heated and stirred at 70°C under a nitrogen atmosphere for 18 hours. Cooled to room temperature and then added 0.4 ml methyl iodide dropwise with stirring which was continued at 50°C for 3 hours. The reaction mixture was then treated by cooling to room temperature, followed by the addition of 15 ml water. The mixture was extracted with 3 x 20 ml of CH_2Cl_2. The organic layers were combined, washed with brine, dried and evaporated to yield a white crystalline residue. Recrystallization from ethyl acetate/CH_2Cl_2 yielded a pure white solid, mp 246-248°C.

Anal. Calcd. for $C_{30}H_{44}N_2O_2 \cdot 0.3H_2O$

Calcd. C, 76.65; H, 9.56; N, 5.95

Found C, 76.50; H, 9.75; N, 5.84

Mass spectroscopy showed a molecular weight of 464.

EXAMPLE 18

Synthesis of 17β-(N-2-adamantylcarbamoyl)-3-oxo-4-methyl-4-aza-5α-androstane

17β-(N-2-adamantylcarbamoyl)-4-methyl-4-aza-androsten-1-en-3-one, (200 mg) as prepared in Example 17, were placed into 25 ml absolute ethanol with 200 mg 30% Pd/C hydrogenation catalyst. The suspension was rocked overnight under 40 psig hydrogen pressure.

The suspension was filtered, and the filtrate evaporated to dryness. The residue was recrystallized from hot ethyl acetate to give a white crystalline solid, mp. 113-115°C. Calcd. for $C_{32}H_{50}N_2O_3 \cdot 0.5$ EtOAc

Calcd: C, 75.25, H, 9.86, N, 5.48

Found C, 75.07; H, 9.52; N, 5.28

Mass spectroscopy depicted a molecular weight of 466 for the non-solvated molecule.

EXAMPLE 19

Synthesis of 17β-(N-methyl-N-2-adamantyl)carbamoyl-4-methyl-4-aza-androst-1-en-3-one

17β-(N-2-adamantyl)carbamoyl-4-aza-androst-1-en-3-one (5.0 g) and 1.5 g sodium hydride in 100 ml dry DMF were stirred under dry nitrogen for 3 hours at 40°C. The reaction was cooled to room temperature and about 4 ml of methyl iodide was added dropwise and allowed to stir at room temperature for one hour. The reaction was cooled in an ice bath and a large excess of about 250 ml, water was added. The aqueous mixture was extracted with CH_2Cl_2 (3 x 100 ml), the organic extracts combined, washed with H_2O, brine, and then evaporated to dryness to yield crude product. The crude product was eluted on an HPLC column (Si gel) with 10/1 acetone/CH_2Cl_2 to yield 2 peaks having retention times of 3 CV(B) and 3.8 CV(A). Peak (A) was analyzed as per the 4-methylaza titled product of Example 15. The second product (B) was analyzed as the 4-methylaza-17β-(N-methyl-N-2-adamantyl/carbamoyl analog, i.e. the titled compound, mp. 163-165. Calcd. for $C_{31}H_{46}N_2O_2$

Calcd. C, 77.77; H, 9.68; N, 5.85

Found C, 77.29; H, 9,79; N, 5.77

Mass spectrometry showed a molecular weight of 478.

EXAMPLE 20

Synthesis of 17β-(N-methyl-N-2-adamantylcarbamoyl)4-aza-4-methyl-androstan-3-one

The crude reaction mixture from Example 19 (4.6 g) was dissolved in 200 ml ethanol and together with 1.0 g 30% Pd/C was hydrogenated under 40-45 Psig a hydrogen atmosphere at room temperature overnight. The mixture was filtered, residue washed with ethanol. The ethanol solution was evaporated to dryness to yield a crude mixture. Recrystallized from CH_2Cl_2/diethyl ether/hexane to yield 800 mg of the pure monomethyl androstane compound of Example 16, mp 113-115°C. Second and third crops were combined with mother liquor and treated by HPLC as in Example 17 to yield the dimethylated title compound, mp 180-182°C.

Anal. Calcd. for $C_{31}H_{48}N_2O_2$

Calcd. C, 77.45; H, 10.06; N, 5.83

Found C, 77.26; H, 9.87; N, 5.82

Mass spectrometry showed a molecular weight of 480.

EXAMPLE 21

N-t-Butyl Androst-3,5-diene-17β-carboxamide-3-Carboxylic Acid

(a) N-t-butyl androst-3,5-diene-3-bromo-17β-carboxamide

To a solution of oxalic acid (0.0011 mol, 0.1 g) and oxalyl bromide (0.0211 mol, 3 ml) in 15 ml of sieve dried toluene was added over a one hour period 1 g (0.003 mol) of androst-4-ene-3-one 17β-carboxylic acid. The reaction was stirred at room temperature for 2 hours and then it was concentrated in vacuo. The excess oxalyl bromide was removed by azetoroping with toluene. The resulting brown oil was redissolved in toluene, cooled to 0°C and then 10 ml t-butylamine (7.0 g) in 30 ml of toluene was added dropwise over 15 minutes. Once the addition was complete, the reaction was stirred at 0°C for 15

minutes and then it was kept at -20°C for 19 hours. The reacton mixture was allowed to warm to room temperature and then stirred at 25°C for one hour. The volatiles were removed in vacuo. The residue was partitioned between chloroform/water, the layers were shaken together and separated and then the aqueous phase was back-extracted twice with chloroform. The combined organic extracts were washed with water (2x) and then dried with anhydrous magnesium sulfate. The crude product was purified by flash chromatography on silica, eluting with 20% ethyl acetate in hexane, to give 1.06 g of the title compound, a white solid.

(b) N-t-Butyl Androst-3,5-diene-17β-carboxamide3-carboxylic acid

To a solution of N-t-Butyl Androst-3,5-diene-3-bromo-17β-carboxamide (0.5 g, 0.00115 mol) in 5 ml of tetrahydrofuran, cooled to -78°C (dry ice/acetone bath) under argon, was added dropwise 1.5 ml (0.00375 mol) of a 2.5 M solution of n-butyl lithium in hexane. The reaction mixture was stirred at this temperature for one hour and then carbon dioxide was bubbled into the reaction for 45 minutes, via a concentrated sulfuric acid tower. The reaction mixture was allowed to warm to room temperature and then it was diluted with water, aqueous HCl solution and chloroform. The layers were shaken together and separated, with the aqueous phase being back-extracted with chloroform (2x). The combined organic extracts were washed with water (2X), and brine (1 x) and then dried with anhydrous magnesium sulfate. The solvents were removed under reduced pressure give 0.6 g of a crude solid. This material was slurried with hexane and a white solid was isolated (0.43 g). The title compound was recrystallized from acetonitrile, m.p. 247°-250°.

EXAMPLE 22

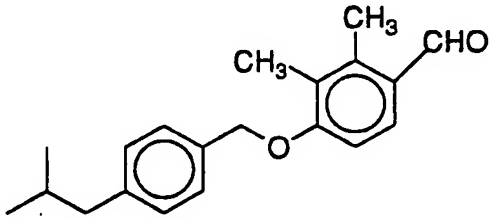
17β-Benzoyl-Androst-3,5-diene-3-Carboxylic Acid

The title compound is made by reacting 17β-carbomethoxy-androst-3,5-diene-3-protected carboxylic acid in e.g.,

THF, with phenyl magnesium bromide under standard Grignard conditions. Standard workup procedure yields the title compound, m.p.222-225°C.

REFERENCE EXAMPLE 1

Synthesis of 4-(4-isobutylbenzyloxy)-2,3-dimethylbenzaldehyde

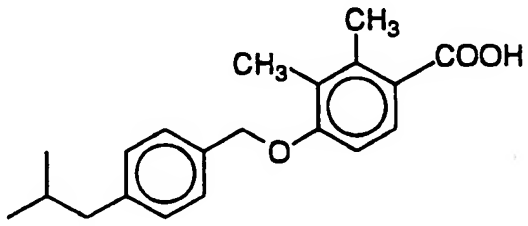


A mixture of 4-hydroxy-2,3-dimethylbenzaldehyde (220 mg), 4-isobutylbenzyl bromide (341 mg), potassium carbonate (1.38 g) and ethyl methyl ketone (10 ml) was refluxed for 6 hrs. After cooling, the reaction mixture was diluted with ethyl acetate, the solution was washed with dil hydrochloric acid, water, successively, dried and evaporated. The residue was purified by column chromatography on silica gel (hexane:EtOAc = 10:1) to give the title compound (383 mg) having the following physical data:

TLC: Rf 0.48 (hexane:EtOAc=5:1); NMR: δ7.64 (1H, d), 7.32 (1H, d), 7.16 (1H, d), 5.12 (2H, s), 2.60 (3H, s), 2.48 (2H, d), 2.24 (3H, s), 1.94-1.80 (1H, m), 0.90 (6H, d).

REFERENCE EXAMPLE 2

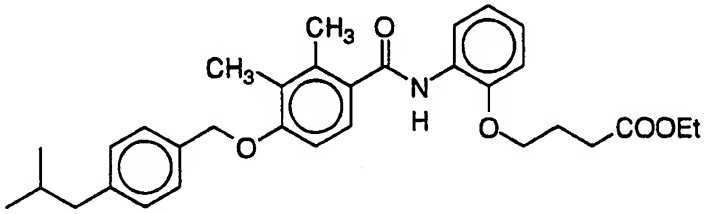
Synthesis of 4-(4-isobutylbenzyloxy)-2,3-dimethylbenzoic acid



A solution of the aldehyde prepared in reference example 1 (380 mg) in acetone (5 ml) was cooled with ice. To the solution, Jones' reagent (2.67 N; 2 ml) was dropped and allowed to stand. The solution was stirred for 1.5 hrs at room temperature. The reaction was stopped by addition of isopropyl alcohol. The crystals deposited were washed with hexane, dried and purified by column chromatography on silica gel (hexane-EtOAc) to give the title compound (328 mg) having the following physical data:
TLC: Rf 0.36 (hexane:EtOAc=2:1); NMR: δ7.80 (1H, d), 7.33 (1H, d), 7.15 (1H, d), 6.90 (1H, d), 5.09 (2H, s), 2.58 (3H, s), 2.48 (2H, d), 2.26 (3H, s), 0.91 (6H, d).

REFERENCE EXAMPLE 3

Synthesis of 4-[2-[4-(4-isobutylbenzyloxy)-2,3-dimethylbenzoyl-aminolphenoxylbutanoic acid ethyl ester

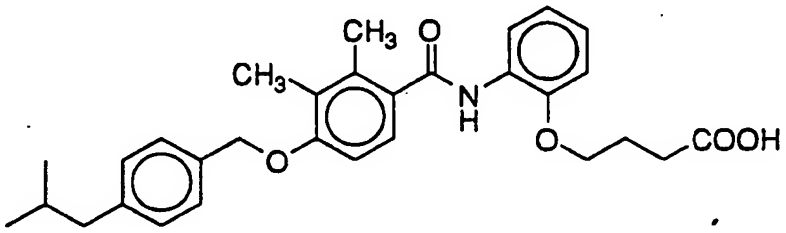


Oxalyl chloride (2 ml) was dropped to a solution of the carboxylic acid prepared in reference example 2 (325 mg) in methylene chloride (2 ml). The solution was stirred for 1 hr and evaporated. To an ice-cooled mixture of ethyl 4-(2-aminophenoxy)butanoate (232 mg), pyridine (1 ml) and methylene chloride (15 ml), the above solution was dropped. The mixture was stirred for 30 mins at the same temperature and for 1 hr at room temperature. The reaction solution was washed with water, dried and evaporated. The residue was purified by column chromatography on silica gel (hexane:EtOAc = 5:1) to give the title compound (383 mg) having the following physical data:
TLC: Rf 0.5 (hexane:EtOAc=3:1); NMR: δ 8.58-8.48 (1H, m), 8.05 (1H, s), 7.34 (H, d), 7.16 (1H, d), 7.08- 6.96 (2H, m), 6.90-6.80 (2H,

m), 5.07 (2H, s) 4.14-3.96 (4H, m), 2.49 (2H, d), 2.44 (3H, s), 1.18 (3H, t), 0.91 (6H, d).

REFERENCE EXAMPLE 4

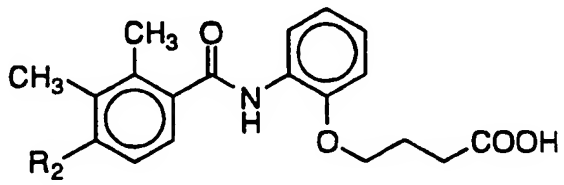
Synthesis of 4-[2-[4-(4-isobutylbenzyloxy)-2,3-dimethylbenzoyl-amino]phenoxy]butanoic acid



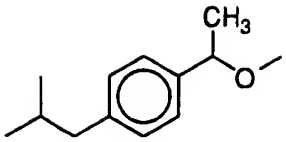
1N aq. Solution of lithium hydroxide (3 ml) was added to a solution of the ester prepared in Reference Example 3 (380 mg) in dimethoxyethane (8 ml). The mixture was stirred for 30 mins at 50°C. After reaction, the solution was neutralized with dil. hydrochloric acid and was extracted with ethyl acetate. The extract was dried and evaporated. The residue obtained was recrystallized from hexane to give the title compound (317 mg) having the following physical data: TLC: Rf 0.26 (hexane:EtOAc = 1:1): mp: 143°C.

REFERENCE EXAMPLE 5

By the similar procedure as reference examples 1, 2, 3 and 4, the following compound was made, 4-[2-[4-[1-(4-isobutylphenyl)-ethoxy)-2,3-dimethylbenzoylamino]phenoxy]butanoic acid, having the structural formula:



where R_2 is



in which the Rf value is 0.37 (hexane:EtOAc = 1:1), and the mass spectrum exhibited m/z values of 503, 345.

REFERENCE EXAMPLE 6

(-)-4-[2-(4-[1-(4-isobutylphenyl)ethoxy]-2,3-dimethylbenzoylamino-phenoxy]butanoic acid

The compound prepared above in reference example 5, (403 mg) and cinchonidine (2.36 g) were dissolved into acetone (70 ml) with heating. The solution was allowed to stand to give white crystals. The crystals were gathered by filtration and purified by recrystallization from acetone four times. The white crystals obtained were dissolved into chloroform. The solution was wahsed with dil. hydrochloric acid. The oily layer was washed with water, dried and evaporated to give the title compound having the following physical data:
Appearance: white crystal;
Optical angle of rotation: $[a]_D$-39.6° (c=1, $CHCl_3$)

REFERENCE EXAMPLE 7

Sodium salt of (-)-4-[2-(4-[1-(4-isobutylphenyl)ethoxy]-2,3-dimethylbenzoylamino)phenoxy]butanoic acid

The compound prepared in Reference Example 6 was dissolved into methanol. The equivalent molar of an aq. Sodium hydroxide solution was added and evaporated to give the title compound having the following data:
IR: ν 3050, 1750, 1580, 1560, 1510, 1445, 1260, 1090, 1020, 740

cm-1.

FORMULATION EXAMPLE

The following components are admixed in conventional method and punched out to obtain 100 tablets each containing 50 mg of active ingredient.

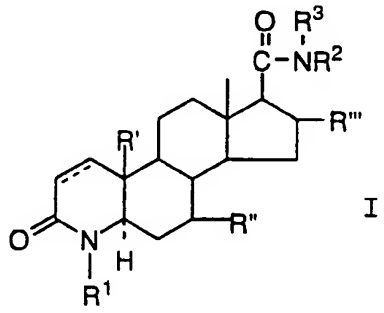
4-[2-[4-[1-(4-isobutylphenyl)ethoxy)-2,3-dimethylbenzoylamino)phenoxy] butanoic acid	5 g
Cellulose calcium gluconate (disintegrating agent)	0.2 g
Magnesium stearate (lubricating agent)	0.1 g
Microcrystaline cellulose	4.7 g

Compounds of formula I may also be used in combination with the compounds 4-[2-[4-(4-isobutylbenzyloxy)-2,3-dimethylbenzoyl-amino]phenoxy]butanoic acid and 4-[2-(4-[1-(4-isobutylphenyl)-ethoxy]-2,3-dimethylbenzoylamino-phenoxy]butanoic acid and the therapeutically active stereoisomers thereof as well as the pharmaceutically acceptable salts and esters thereof for the treatment of human patterned alopecia.

WHAT IS CLAIMED IS:

1. A method of treating humans for patterned alopecia, who are in need of such treatment, which comprises administration of a therapeutically effective amount of:

(A) a compound of the formula



I

wherein

the dotted line represents a double bond when present;

R^1 and R^3 are independently hydrogen, methyl or ethyl;

R^2 is a hydrocarbon radical selected from substituted or unsubstituted:

(a) straight or branched chain alkyl of from 1-12 carbons,

(b) cycloalkyl of from 3-12 carbons,

(c) -C_{1-3} alkyl-C_{3-12} cycloaklyl,

(d) aralkyl of from 7-12 carbons, and

(e) monocyclic aryl,

with the proviso that R^2 is not t-butyl when R^1 and R^3 are H;

R' is hydrogen or methyl;

R" is hydrogen or β-methyl; and

R'" is hydrogen, α-methyl or β-methyl;

or a pharmaceutically acceptable salt or ester thereof, administered topically or orally; and

(B) a potassium channel opener selected from the group consisting of minoxidil, cromakalim, pinacidil, a compound selected from the

classes of s-triazine, thiane-1-oxide, benzopyran, or pyridinopyran derivatives, or a pharmaceutically acceptable salt thereof.
(B) minoxidil or a pharmaceutically acceptable salt thereof,
administered topically.

2. The method according to Claim 1 wherein the potassium channel opener is minoxidil or a pharmaceutically acceptable salt thereof.

3. The method according to Claim 1 wherein:
the dotted line is a double bond;
R^1 is hydrogen or methyl; R^3 is hydrogen;
R^2 is selected from
(a) branched chain alkyl of from 4-12 carbons,
(b) cycloalkyl of from 4-12 carbons,
(c) aralkyl of from 7-12 carbons, and
(d) phenyl, unsubstituted or substituted by methyl, chloro or fluoro;
and R" and R"' are hydrogen.

4. The method of claim 1 wherein the dotted line is a double bond and R^2 is a substituted or unsubstituted 1-, 2-adamantyl, 1-, 2-adamantylmethyl, 1-, 2- or 7-norbornanyl, or 1-, 2- or 7-norbornanylmethyl, wherein the substituents are selected from one or more of: C_1-C_4 linear or branched alkyl; nitro; oxo; C_7-C_9 aralkyl; $(CH_2)_n$ COOR wherein n is 0, 1 or 2 and R is H or C_1-C_4 linear or branched alkyl; CH_2OH; OH; OR^a wherein R^a is C_1-C_4 linear or branched alkyl; halo; COOH; $COOR^b$ wherein R^b is linear or branched C_1-C_4 alkyl; -$CONH_2$; CH_2NH_2; CH_2NHCOR^c wherein R^c is C_1-C_4 linear or branched alkyl; phenyl; p-nitrophenyl , p-aminophenyl and p-sulfophenyl; or cyano.

5. The method according to Claim 1 wherein the compound of Formula I is selected from:
17β-(N-tert-butylcarbamoyl)-4-aza-4-methyl-5α-androst-1-en-3-one;

17β-(N-isobutylcarbamoyl)-4-aza-5α-androst-1-en-3-one;
17β-(N-tert-octylcarbamoyl)-4-aza-4-methyl-5α-androst-1-en-3-one;
17β-(N-tert-octylcarbamoyl)-4-aza-5α-androst-1-en-3-one;
17β-(N-1,1-diethylbutylcarbamoyl)-4-aza-4-methyl-5α-androst-1-en-3-one;
17β-(N-1,1-diethylbutylcarbamoyl)-4-aza-5α-androst-1-en-3-one;
17β-(N-tert-hexylcarbamoyl)-4-aza-4-methyl-5α-androst-1-en-3-one;
17β-(N-tert-hexylcarbamoyl)-4-aza-5α-androst-1-en-3- one;
17β-(N-2-adamantylcarbamoyl)-4-aza-5α-androst-1-en-3-one,
17β-(N-1-adamantylcarbamoyl)-4-aza-5α-androst-1-en-3-one,
17β-(N-2-norbornylcarbamoyl)-4-aza-5α-androst-1-en-3-one,
17β-(N-1-norbornylcarbamoyl)-4-aza-5α-androst-1-en-3-one,
17β-(N-1-adamantylcarbamoyl)-4-aza-5α-androstan-3-one;
17β-(N-1-adamantylcarbamoyl)-4-methyl-4-aza-5α-androst-1-en-3-one;
17β-(N-1-adamantylcarbamoyl)-4-methyl-4-aza-5α-androstan-3-one;
17β-(N-1-adamantylmethylcarbamoyl)-4-aza-5α-androst-1-en-3-one;
17β-(N-2-adamantylcarbamoyl)-4-aza-5α-androstan- 3-one;
17β-(N-methyl-N-2-adamantylcarbamoyl)-4-methyl-4-aza-androstan-3-one;
17β-(N-2-adamantylcarbamoyl)-4-methyl-4-aza-5α-androstane-3-one;
17β-(N-2-adamantylcarbamoyl)-4-methyl-4-aza-5α-androst-1-en-3-one;
17β-(N-methyl-N-2-adamantyl)carbamoyl-4-methyl-4-aza-androst-1-en-3-one;
17β-(N-(3-methyl)-1-adamantyl-carbamoyl)-4-aza-4-methyl-5α-androst-an-3-one;
17β-(N-exo-2-norbornanylcarbamoyl)-4-aza-4-methyl-5α-androst-1-en-3-one; and
17β-(N-exo-2-norbornanylcarbamoyl)-4-aza-5α-androst-1-en-3-one.

6. The method according to Claim 5 wherein the compound of formula I is 17β-(N-tert-butylcarbamoyl)-4-aza-4-methyl-5α-androst-1-en-3-one.

7. The method according to Claim 1 wherein the compound of formula I is orally administered.

8. The method according to Claim 1 wherein the compound of formula I is topically administered.

9. The method according to Claim 1 wherein the compound of formula I is administered at a daily dosage of from 1 to 2,000 mg per person.

10. The method according to Claim 9 wherein the compound of formula I is administered at a daily dosage of from 1 to 20 mg per person.

11. The method according to Claim 1 wherein minoxidil is topically applied to the scalp in a concentration of about 1 to 5% by weight in an inert vehicle adapted for topical application.

12. A topical pharmaceutical composition for the treatment of patterned alopecia comprising a therapeutically effective amount of minoxidil or a pharmaceutically acceptable salt thereof and a compound of the structural formula I as defined in Claim 1, in a vehicle adapted for topical application.

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US[redacted]176

A. CLASSIFICATION OF SUBJECT MATTER
IPC(5) :A61K [redacted], 31/505
US CL :514/284, 275
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/284, 275

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS, DIALOG, APS- COMPOUNDS OF FORMULA I , MINOXIDIL AND POTASSIUM CHANNEL OPENERS IN THE TREATMENT OF BALDNESS, AND HAIR AND SKIN DISORDERS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,596,812 (CHIDSEY, III ET AL.) 24 JUNE 1986, SEE ESPECIALLY COLUMN 1, LINES 21-23.	1-12
Y	US, A, 4,760,071 (RASMUSSON ET AL.) 26 JULY 1988, SEE ESPECIALLY THE ABSTRACT AND COLUMN 1, LINES 17-66.	1-12
Y	US, A, 4,377,584 (RASMUSSON ET AL.) 22 MARCH 1983, SEE ESPECIALLY THE ABSTRACT AND COLUMN 1, LINES 17-66.	1-12

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be part of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 APRIL 1994	APR 25 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer M. MOEZIE Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNAT[redacted]AL SEARCH REPORT

[redacted]nal application No.
PC[redacted]S94/00176

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WPI ABSTRACT, ISSUED FEBRUARY 02, 1992, BONTE ET AL., "NEW DERMATOLOGICAL COMPOSITIONS CONTAINING COLEUS EXTRACTS- ARE USED TO ENCOURAGE PIGMENTATION OF THE SKIN OR HAIR TO TREAT DISORDERS OF MELANOGENESIS", SEE WPI 008998345, WPI ACC NO: 92-125619/16, X-RAM ACC NO: C92-058565, FR. PAT. NO. 2,665,637.	12
Y	CHEMICAL ABSTRACTS VOLUME 116, NO.24, ISSUED 20 FEBRUARY 1992, DIANI ET AL., "HAIR GROWTH STIMULANTS CONTAINING POTASSIUM CHANNEL OPENERS AND 5-ALPHA-REDUCTASE INHIBITORS", PAGES 1-17, ABSTRACT NO. 241714e, WO 92/02,225.	1-12